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COMMENTS OF PFIZER INC ON DOCKET NO. 2004P-0261: Prevent Pfizer Inc from marketing a generic version of Accupril® until after the expiration of Teva's 180-day exclusivity period

On behalf of Pfizer Inc ("Pfizer"), the undersigned submit these comments in response to the above-referenced Citizen Petition filed by Teva Pharmaceuticals USA, Inc. ("Teva"). In that petition, Teva seeks to prevent Pfizer from launching an unbranded version of ACCUPRIL® (quinapril hydrochloride), a drug for which Pfizer holds the approved NDA. As discussed in these comments, Teva's request is unsupported by, and in fact inconsistent with, the Federal Food, Drug and Cosmetic Act ("FDCA") and FDA regulations. Thus, Teva's petition should be denied.

I. INTRODUCTION

Teva was the first to file an Abbreviated New Drug Application ("ANDA") with a paragraph IV certification seeking to market quinapril hydrochloride products based on the safety and efficacy data contained in Pfizer's NDA. In accordance with the provisions of the Hatch-Waxman Amendments, Warner-Lambert, now a subsidiary of Pfizer Inc, initiated patent litigation against Teva in the United States District Court for the District of New Jersey. *Warner-Lambert Co. v. Teva Pharmaceuticals USA,* Docket No. 2:99cv922 (D.N.J. filed March 2, 1999). On October 2, 2003, that court awarded Warner-Lambert partial summary judgment, ruling that the formulation patent at issue is valid and that Teva's ANDA product infringes that patent. In May 2004, the court conducted a trial on issues of obviousness of certain patent claims and on Teva's allegations of inequitable conduct and currently has the case under advisement.

Teva's petition seeks to block Pfizer from marketing unbranded quinapril hydrochloride in order to limit competition with Teva's product – should it come to market – until the conclusion of the 180-day period during which FDA is precluded from approving subsequent paragraph IV ANDAs under Section 505(j)(5)(B)(iv) of the Federal Food, Drug and Cosmetic Act ("FDCA"). Pfizer's unbranded quinapril

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hydrochloride product[1] is not subject to the 180-day gating provision upon which Teva relies, however. Section 505(j)(5)(B)(iv) blocks only paragraph IV ANDAs. Pfizer will market unbranded quinapril hydrochloride *under its original NDA for* Accupril®, not under a paragraph IV ANDA. Nevertheless, Teva's petition asks FDA to treat Pfizer's drug as if it were marketed under a paragraph IV ANDA and thus deem it to be blocked by Teva's "prior" paragraph IV application.

Specifically, Teva demands that FDA impose on Pfizer new and contrived requirements for amending Pfizer's Accupril® NDA to reflect the *pro forma* changes in tableting and labeling that Pfizer's prospective launch of unbranded quinapril hydrochloride will entail. Teva asks FDA to:

- "require Pfizer to submit a pre-approval supplemental NDA . . . before it markets or distributes any version of its Accupril® product which has been changed, by way of any manufacturing, labeling, packaging, or product code changes, such that the product purports to be, resembles or could be confused with, a generic (unbranded) versions of Accupril®, if a product with such changes is proposed to be distributed prior to the expiration of Teva's 180-day exclusivity period for generic quinapril drug products " Teva Petition at 1;

- delay FDA's approval of such NDA supplement until expiration of "Teva's 180-day generic exclusivity period for generic quinapril drug products." *Id.*;

- on a going forward basis, create a pre-approval procedure whereby, upon acceptance of the first paragraph IV ANDA for a reference listed drug, FDA would notify the NDA holder for the innovator drug that any "change[], by way of any manufacturing, labeling, packaging, or product code changes, such that the product purports to be, resembles or could be confused with, a generic (unbranded) version" of the approved NDA drug would need to be the subject of an approved supplemental NDA; *Id.* at 1, 13;

- inform the NDA holder that no such supplemental NDA will be approved from the time of the filing of the first paragraph IV ANDA referencing the

[1] Pfizer expects to launch unbranded quinapril hydrochloride tablets through its Greenstone subsidiary, commencing with Teva's launch of its generic quinapril product.

NDA holder's approved drug until the expiration or forfeiture of the ANDA approval delay period provided by Section §505(j)(5)(B)(iv), unless that first ANDA filer permits the NDA holder to make the product change. *Id. at 14.*

The scheme Teva proposes is an attempt to create a new set of regulated drug products under the FDCA for Teva's own financial gain. The FDCA does not contemplate or recognize treating a product approved by FDA under an NDA differently because it is distributed in unbranded trade dress, or because it is priced competitively with ANDA-approved products, be they first or last on the market. Teva's proposal is plainly foreclosed by the language of the FDCA, would inject FDA into areas wholly outside its public health mission, and is directly contrary to one of the central goals of Hatch-Waxman – to promote price competition in prescription drugs upon expiration or resolution of the constitutionally-protected patent rights of an NDA holder.

II. TEVA'S ATTEMPT TO INFLATE THE 180-DAY STATUTORY DELAY PERIOD APPLICABLE TO LATER PARAGRAPH IV ANDA APPLICANTS INTO A REQUIREMENT THAT FDA SUPPRESS PRICE COMPETITION FROM NDA HOLDERS IS CONTRARY TO THE FDCA.

A. The Plain Language of the FDCA Clearly Defines and Limits The Scope Of The "Exclusivity" Afforded by Section 505(j)(5)(B)(iv).

Under the plain and unambiguous language of Section 505(j)(5)(B)(iv), only subsequent paragraph IV ANDAs, but not NDAs, are subject to deferred FDA approval:

> If *the application contains a certification described in subclause (IV) of paragraph (2)(A)(vii) and is for a drug for which a previous application has been submitted under this subsection continuing [sic] such a certification*, the application shall be made effective not earlier than one hundred and eighty days after –
>
> (I) the date the Secretary receives notice from the applicant under the previous application of the

> first commercial marketing of the drug under the previous application, or
>
> (II) the date of a decision of a court in an action described in clause (iii) holding the patent which is the subject of the certification to be invalid or not infringed,
>
> whichever is earlier.

21 U.S.C. §355(j)(5)(B)(iv) (emphasis added).[2]

The plain language of the statute instructs FDA to delay approving *only*: (A) other Abbreviated New Drug Applications; (B) that also contain a paragraph IV certification to a patent claiming the listed drug; and (C) that were filed later than the first ANDA containing such a paragraph (IV) certification. Where an application meets each of those conditions, Congress has *prohibited* FDA from approving that ANDA until 180 days after the earlier of either (1) commercial marketing of the drug by the qualifying first ANDA applicant or (2) a relevant court decision finding the patent at issue to be invalid or not infringed. The 180-day bar on approval, however, does not apply outside those circumstances.

In fact, the FDCA contemplates numerous routes to market that are not subject to the 180-day restrictions imposed by Section 505(j)(5)(B)(iv), despite the potential that products approved through such routes might provide immediate competition to the first-filed ANDA applicant. For example, applications under Section 505(b)(2) of the FDCA, while required to provide patent certifications

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[2] The Medicare Prescription Drug, Improvement and Modernization Act of 2003 ("MMA") significantly revised the provisions of §505(j)(5)(B)(iv). Those provisions do not apply to Teva's ANDA as it was pending prior to the enactment of the MMA. However, it is significant that Congress did not change the operative language defining those applicants against whom section 505(j)(5)(B)(iv) insulated the first-filer from competition. Subject to "forfeiture events" set forth in the statute, the MMA states that if an ANDA "*contains a certification described in paragraph (2)(A)(vii)(IV) and is for a drug for which a first applicant has submitted an application containing such a certification*, the application shall be made effective on the date that is 180 days after the date of the first commercial marketing of the drug (including the commercial marketing of the listed drug) by any first applicant." Medicare Prescription Drug, Improvement and Modernization Act, § 1102(a)(emphasis added).

identical to those required of ANDA applicants, are not subject to the approval requirements of Section 505(j)(5)(B)(iv). *Compare* 21 C.F.R. § 314.107(b)&(d) with § 314.107(c)(applying the same effective date provisions to 505(b)(2) applications and ANDAs, except for subsection (c), governing the 180-day first-filer preference among ANDA paragraph IV certifiers). Similarly, where a method of use patent is at issue, an ANDA applicant who chooses to "carve out" the patented use from its labeling rather than certify to the patent's invalidity or non-infringement is not subject to Section 505(j)(5)(B)(iv). *See* 21 U.S.C. § 355(j)(2)(A)(viii). These provisions further reinforce what the language and structure of the statute have made clear since Hatch-Waxman was first implemented: the 180-day "exclusivity" provided to the first ANDA filer to certify as to the invalidity or non-infringement of an existing, relevant patent serves to prevent market entry and competition *only* from later, similarly certifying ANDAs that may benefit from the first filer having taken the risk of challenging the patent at issue.

The statutor y language governing the 180-day delay in approval of subsequent ANDAs in §505(j)(5)(B)(iv) unambiguously precludes the relief requested by Teva. The plain language of the statute blocks *only* subsequent paragraph IV ANDAs. The statute has no application to Pfizer's distribution of quinapril hydrochloride tablets under Pfizer's NDA.

B. Subsequent Judicial Interpretation Makes Clear That FDA May Not Impose Limitations Under Section 505(j)(5)(B)(iv) Not Set Forth By Congress.

Courts have already taken FDA to task for going beyond the statutory language of Hatch-Waxman and creating rights and imposing obligations that were not set forth by Congress. Courts have repeatedly found that these deviations from the statute are beyond the Agency's authority. While FDA is entitled to deference in filling "gaps" in the statutory scheme to which Congress has not spoken, such gap-filling is beyond its authority when it "cannot be reconciled with the literal language of the statute and alters the statutory scheme in a number of ways that do not clearly serve congressional intent." *See, e.g., Mova Pharmaceuticals Corp. v Shalala,* 140 F.3d 1060 (D.C. Cir. 1998). In *Mova,* the D.C. Circuit invalidated under *Chevron* an FDA regulation requiring the first filer to achieve a patent victory in order to be entitled to the 180-day delay period. Subsequent courts have overturned FDA's interpretation of "a court decision" as contrary to the plain

language of the statute; *Teva Pharmaceuticals, USA, Inc. v. FDA*, 182 F.3d 1099 (D.C. Cir. 1999); *Torpharm, Inc. v. Shalala*, 1997 WL 33472411 (D.D.C. Sep 15, 1997). These decisions make clear that the Agency's role in administering section 505(j)(5)(B)(iv) is to apply the language as written. *Mova Pharmaceuticals Corp. v Shalala,* 140 F.3d 1060 (D.C. Cir. 1998). As the 4th Circuit noted in reaching a conclusion identical to that reached by the D.C. Circuit in *Mova,*

> Congress has plainly laid out the requirements for the 180-day exclusivity period in the statute (albeit in tortured language), and, thus, our inquiry into Congressional intent must end there. Having found the exclusivity requirements embodied in the statutory language of 21 U.S.C.A. § 355(j)(4)(B)(iv) clear and conclusive, we are bound to hold invalid any attempt to alter the terms of that statute.

Granutec, Inc. v. Shalala, 1998 U.S. App. LEXIS 6685 at *20 (April 3, 1998) (unpublished disposition).

The plain language governs and defeats Teva's effort to turn the benefit it derives from the statutory bar against final approval of other ANDA applicants into a prohibition on competitive marketing of the NDA holder's product.

III. TEVA'S REQUESTED RELIEF UNDERMINES THE POLICIES BEHIND HATCH-WAXMAN.

Teva's attempt to have FDA regulate market competition between ANDA and NDA holders lacks policy support, as well as legal foundation, in the Hatch-Waxman provisions. One end goal of Hatch-Waxman was to promote price competition for the benefit of consumers to the extent compatible with pioneer patent rights.[3] Teva's petition is a flagrant effort to stifle price competition -- to

[3] *In re Barr Labs., Inc.,* 289 U.S. App. D.C. 187, 930 F.2d 72, 76 (D.C. Cir.), *cert. denied*, 502 U.S. 906, 116 L. Ed. 2d 241, 112 S. Ct. 297, 112 S. Ct. 298 (1991). The Hatch-Waxman Amendments "emerged from Congress' efforts to balance two conflicting policy objectives: to induce name-brand pharmaceutical firms to make the investments necessary to research and develop new drug products, while simultaneously enabling competitors to bring cheaper, generic copies of those drugs to market." *Mylan, Inc. v. Shalala,* 81 F. Supp. 2d 30 (D.D.C. 2000)(citing *Abbott Labs. v. Young,* 287 U.S. App. D.C. 190, 920 F.2d 984, 991 (D.C. Cir. 1990) (Edwards, J., dissenting) (citations omitted), cert. denied, *502 U.S.* 819 (1991)).

Teva's benefit and the public's detriment -- without foundation in FDA's public health and safety mandate or patent policy. When NDA holders choose to use their manufacturing expertise to compete on price with ANDA holders, the pro-competitive policies of the Hatch-Waxman provisions are not, as Teva would have it, retarded; they are clearly advanced.

Because Section 505(j)(5)(B)(iv) imposes no limitations on NDA holders, it is clear that Congress intended that the first-filer would receive a limited head start as to other ANDAs, but would be forced to compete with the approved NDA product. While Teva suggests that such competition is less than fair because the approved product has had the market to itself prior to the first-filer's entry, the innovator's market exclusivity is based on the investment made by the NDA holder in researching, testing, and demonstrating the safety and efficacy of the drug product in the first instance.

Both the Constitution and Congress recognize the importance of providing investors in new inventions a marketplace protected from all imitators through the patent system in order to allow that investment to be rewarded. An ANDA applicant's efforts in assembling an ANDA, demonstrating bioequivalence, and challenging existing patents may be something Congress sought to encourage, but Congress never intended, and never gave FDA authority, to regulate competition between the ANDA applicant and the NDA holder.

IV. TEVA'S INVITATION FOR FDA TO UNILATERALLY CREATE AN ILL-DEFINED REGULATORY SCHEME FOR SCREENING AND APPROVAL OF PREVIOUSLY-APPROVED NDA PRODUCTS IS CONTRARY TO FDA'S PUBLIC HEALTH MISSION.

As noted above, Teva's petition requests that FDA (1) "require Pfizer to submit a pre-approval supplemental NDA . . . before it markets or distributes any version of its Accupril® product which has been changed, by way of any manufacturing, labeling, packaging, or product code changes, such that the product purports to be, resembles or could be confused with, a generic (unbranded) versions of Accupril®, if a product with such changes is proposed to be distributed prior to the expiration of Teva's 180-day exclusivity period for generic quinapril drug products"; (2) delay FDA's approval of such NDA supplement until expiration of "Teva's 180-day generic exclusivity period for generic quinapril drug products;" (3) create a pre-approval procedure whereby, upon acceptance of the first paragraph IV

ANDA for a reference listed drug, FDA would notify the NDA holder for the innovator drug that any "change[], by way of any manufacturing, labeling, packaging, or product code changes, such that the product purports to be, resembles or could be confused with, a generic (unbranded) version" of the approved NDA drug would need to be the subject of an approved supplemental NDA; and (4) inform the NDA holder that no such supplemental NDA will be approved from the time of the filing of the first paragraph IV ANDA referencing the NDA holder's approved drug until the expiration or forfeiture of the ANDA approval delay period provided by Section §505(j)(5)(B)(iv), unless that first ANDA file permits the NDA holder to make the product change.

Unable to find any statutory language to support its proposed regulatory scheme in those provisions of the FDCA that govern FDA's approval of NDAs and ANDAs, Teva turns to Section 506A of the Act, added by the FDA Modernization Act of 1997 to ensure that FDA has the opportunity to review and approve major changes to manufacturing processes; i.e., changes to those processes that "have substantial potential to adversely affect the identity, strength, quality, purity or potency of the drug *as they may relate to the safety or effectiveness of such drug.*" *See* FDCA Section 506A(c)(2) (emphasis added). Teva concedes that Section 506A(d) provides FDA with the discretion to create categories of "*manufacturing* changes that are not major" – changes for which the agency may forego any preapproval whatsoever. In fact, FDA has only last month done just that, and determined that each of the changes Teva would have FDA evaluate are not major, and do not require an NDA supplement. Teva's proposed scheme disregards the mandate of Section 506A and would detract from, not serve, FDA's public health mission.

A. Teva's Proposed Criteria for Requiring FDA Approval of Supplemental NDAs Contradicts The Language and Intent of 506A and Interferes With FDA's Risk-Based Approach to the Regulation of Pharmaceuticals.

On April 8, 2004, FDA issued its final rule amending its regulations governing the submission and approval of supplements to NDAs and ANDAs already approved under Section 505 of the Act. *Supplements and Other Changes to An Approved Application; Final Rule,* 69 Fed. Reg. 18726 (April 8. 2004). That same day, the Agency also issued its final companion guidance to those regulations, *Guidance to Industry on Changes to an Approved NDA or ANDA; Notice of*

Availability; 69 Fed. Reg. 18768 (April 8, 2004). As FDA noted in the preamble accompanying the final rule, "[t]he publication of this final rule is an important step in the process of adopting a risk-based approach to the regulation of pharmaceuticals." FDA noted that its proposed rule and the accompanying guidance would both enhance public health by focusing agency resources on those changes that had the greatest potential to impact safety and efficacy and promote the goals of FDAMA by reducing the burden on FDA and regulated industry of unnecessary regulatory submissions and reviews:

> The regulations provide for a new approach to regulating post approval manufacturing changes. The approach is based on *the potential for a change to adversely affect the identity, strength, quality, purity, purity or potency of drug products as these factors relate to the safety and effectiveness of the product.* The regulation and companion guidance . . . will provide significant regulatory relief by allowing post approval manufacturing changes to be implemented more rapidly, while still ensuring the identity, strength, quality, purity, and potency of drug products.

69 Fed. Reg. at 18730-31 (emphasis added).

The contrived regulatory process Teva requests in its petition directly conflicts with, and undermines, this rule and its accompanying guidance. Teva's proposals would impose stiffer FDA review requirements for the very same minor manufacturing and labeling changes that the guidance states should be permitted without prior agency review. *See* Guidance at 26. Teva seeks this expanded agency review process not because of concerns for product safety or efficacy, but to implement unlegislated barriers to competition. . FDA should not countenance this wasteful use of its resources, and this unwarranted interference with the agency's recent regulatory reform efforts.

FDA has, where appropriate, made clear that it would not extend its authority and responsibility into areas beyond its public health mandate and

expertise.[4] We respectfully suggest that the protectionist analysis Teva proposes would require FDA to venture into pricing and distribution issues wholly unrelated to the safety and efficacy of the drug. Such forays are undeniably beyond FDA's public health mandate and the express statutory authority provided to it by Congress.

B. The Authorities Cited By Teva Demonstrate That The Relief It Requests Would Violate the FDCA.

Teva relies heavily on *Mylan Pharmaceuticals, Inc. v. Thompson,* 207. F. Supp.2d 476 (N.D.W. Va. 2001) for the proposition that the approved NDA drug may be treated as an ANDA drug product subject to the statutory delay provided by Section 505(j)(5)(B)(iv). *Mylan,* however, addressed only the distinct question of whether a generic company's launch of product supplied by the NDA holder constitutes "commercial marketing" for purposes of triggering the 180-day period. Thus, if at all relevant, *Mylan v. Thompson* stands for the proposition that restrictions on competition with first filers are disfavored and should be confined strictly to the boundaries of statutory language.

Teva also relies on – and misinterprets – FDA's statements made in promulgating its final rules implementing Hatch-Waxman. As Teva notes, FDA originally proposed, but ultimately rejected a regulation that would have allowed FDA to approve *later-filed ANDA applications* prior to expiration of the 30-month litigation stay and the 180-day first-filer delay provision if the owner of the contested patent granted a patent license to another ANDA applicant. As Teva notes, FDA declined to do so, recognizing that it would be contrary to the statutory language for FDA to issue an approval of an ANDA and allow marketing of a previously unapproved drug product out of turn and prior to the expiration of the first-filer's 180-day delay period. FDA has implemented that statutory requirement by refusing to issue a final approval letter to tentatively approved ANDAs until the prescribed statutory delay has expired, regardless of whether the tentatively-approved applicant is able to obtain a license to the patented invention underlying its product.[5] However, nothing in FDA's analysis, or in the language of the FDCA,

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[4] For example, FDA has repeatedly asserted that it has neither the expertise nor resources to evaluate patents submitted for listing pursuant to Sections 505(b)(1) and (j)(7).

[5] Interestingly, while Teva would read that final approval requirement strictly where it serves its needs, it would also encourage FDA to ignore that requirement and issue final approval of Teva's

authorizes FDA to limit or restrict the manner in which the approved NDA product is distributed.

V. FDA SHOULD REJECT ONCE AND FOR ALL THE NOTION THAT ANDA APPLICANTS HAVE ANY PROPERTY RIGHT OR INTEREST IN SECTION 505(j)(5)(B)(IV).

Teva's petition marks the latest attempt by ANDA applicants to distort the limited exclusivity allegedly promised by Section 505(j)(5)(B)(iv). As demonstrated above, neither the language of nor the policy behind that section entitle Teva or other ANDA filers to anything other than FDA's compliance with the specific instructions laid out in that section.

It is incumbent on FDA to once and for all put an end to the notion that an ANDA applicant who wins in the race to file an ANDA with a paragraph IV certification secures a property right to control FDA's approval actions, either as to other ANDA applicants or NDA holders. The allure of "exclusivity", and the distortion of the plain language of Section 505(j)(5)(B)(iv) beyond its terms in other contexts, has resulted in an attempt to convert the availability of a 180-day head start from a Congressionally limited instruction into a "pseudo patent" which can be licensed at will and which FDA must protect without regard to public health considerations. In Docket No. 2004P-0221, Pfizer has filed a Citizen Petition challenging FDA's interpretation of Section 505(j)(5)(B)(iv) to allow a first filer to sell or swap its purported "exclusivity" rights. That petition explains why the Hatch-Waxman amendments confer no property rights on ANDA filers and is attached and incorporated herein. Teva's instant petition further demonstrates the need for FDA to make absolutely clear that FDA will, in performing its duties under the FDCA, provide to ANDA applicants no more and no less than what the Section 505(j)(5)(B)(iv) specifies.

(Continued . . .)
tentatively approved gabapentin product prior to the expiration of another manufacturer's 180-day period. *See Comments of Teva Pharmaceutical Industries, Ltd. and Purepac Pharmaceutical Co.*, Docket 2004P-0227.

VI. CONCLUSION

For the reasons stated herein, FDA should expeditiously deny the above-referenced Citizen Petition, grant the relief sought by Pfizer's Petition filed in Docket No. 2004P-0227, reaffirm its intention to regulate "from the statutory language", clearly repudiate the notion of any rights of property in the 180-day delay period, and reject further efforts to expand the competitive limitations Congress established in 21 U.S.C. §355(j)(5)(B)(iv) beyond those provided by statute.

Respectfully submitted,

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